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Production of amino pyrrolopyrimidine protein kinase inhibitors - and new crystal forms; by Dimroth rearrangement of imino pyrrolopyrimidine obtained by cyclisation of cyano-pyrrole with imine compound
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WO 9843973	A1	19981008	WO 98EP1760	A	19980325	199846	B
AU 9872103	A	19981022	AU 9872103	A	19980325	199910	

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Designated States (National): AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
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AU 9872103	A		C07D-487/04	Based on patent WO 9843973

Abstract (Basic): WO 9843973 A

Production of 4-ar(alk)ylamino-pyrrolo[2,3-d]pyrimidine derivatives (I) and their salts comprises heating a 3-ar(alk)ylamino-4-imino-pyrrolo[2,3-d]pyrimidine (II) or salt in a solvent or solvent mixture. Reactive groups present in (II) are protected if necessary and are cleaved off as a final step. n = 0-5; q = 0 or 1; R1, R2 = H; alkyl optionally substituted by halo, NH2, NH(alkyl), piperazino, N(alkyl)2, phenylamino (optionally ring-substituted by halo, alkyl, OH, alkanoyloxy, alkoxy, COOH, alkoxycarbonyl, CONH2, CONH(alkyl), CON(alkyl)2, CN, NH2, NH(alkanoyl), NH(alkyl), N(alkyl)2 or CF3), OH, alkoxy, CN, COOH, alkoxycarbonyl, CONH2, CONH(alkyl), CON(alkyl)2, SH or A-S(O)m-; phenyl optionally substituted by halo, CF3, alkyl, alkoxy, OCH2CONH2, OCH2COOH, OCH2COO-benzyl, OCH2COO- alkyl, phenyl, NH2, NH(alkanoyl), NH(alkyl), N(alk yl)2, OH, alkanoyloxy, COOH, alkoxycarbonyl, CONH2, CONH(alkyl), CON(alkyl)2, CN or NO2; pyridyl optionally substituted by halo or alkyl; N-benzylpyridinium-2-yl; naphthyl; CN; COOH; alkoxycarbonyl; CONH2; CONH(alkyl); CON(alkyl)2; CONH(benzyl); CHO; alkanoyl; alkenyl; or alkenyloxy; or R1 + R2 = 2-5C alkylene optionally substituted by alkyl; 4-10C alkadienyl optionally substituted by NH2, NH(alkanoyl), NH(alkyl), N(alkyl)2, NO2, halo, OH, alkanoyloxy, COOH, alkoxycarbonyl, CONH2, CONH(alkyl), CON(alkyl)2 or CN; or aza-1,4-alkadienylene with up to 9C; A = alkyl; m = 0-2; R3 = halo; alkyl; CF3; alkoxy; OH; alkanoyloxy; COOH; alkoxycarbonyl; CONH2; CONH(alkyl); CON(alkyl)2; CN; NH2; NH(alkanoyl); NH(alkyl); or N(alkyl)2; R4 = H; alkyl; alkoxycarbonyl; CONH2; CONH(alkyl); or CO N(alkyl)2. All alkyl and derivatives are ''lower''.

Also claimed are: a) crystal forms of 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine (I); b) compounds (II) and their salts where n = 0 or 1; R1 = alkyl, especially Me, phenyl substituted by OH or alkanoylamino, especially

4-(hydroxy or acetylamino)-phenyl, or NH(alkyl), especially CONHMe; R2 = H or alkyl, especially Me; R3 = H or halo, especially meta-positioned and preferably Cl; R4 = alkyl, especially Me; c) imines (IV); d) production of (I) from (II) including the initial step of preparing (II) by reacting a cyanopyrrole (III) (see 'Starting materials') with an imine (IV); e) production of (I) from (II) according to d) and including the preparation of (IV) by reacting an amine (V)with an orthoformate (VI); f) production of (I) from (II) according to d) and including the preparation of (III) by reacting an amino acid (VII) with a reactive acid derivative (VIII) and cyclising the reaction product (X) with malononitrile. (I) are known from EP 682027 and WO 9702266.

USE- (I) are protein kinase inhibitors useful for the treatment of proliferative diseases, e.g. tumours and psoriasis.

ADVANTAGE - The method is very well suited to plant scale production, with (I) being obtained in high yield, e.g. 80-94%, and high purity. Also, the new crystal forms have storage properties which are advantageous for pharmaceutical application.

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Derwent Class: B02

International Patent Class (Main): C07D-487/04

International Patent Class (Additional): A61K- 31/505; C07C-257/12; C07D-209-00; C07D-239-00; C07D-487/04